(i) DBM, (ii) BMP, TGF-β, PDGF, or mixtures thereof, natural or recombinant; and (iii) mixtures of (i) and (ii).

Dt cont

39. The method of claim 33, wherein said one or more bioresorbable, organic, osteogenic components are selected from the group consisting of (i) DBM, (ii) BMP, TGF-β, PDGF, or mixtures thereof, natural or recombinant; and (iii) mixtures of (i) and (ii).

Remarks

1. To begin, Applicants wish to express their gratitude for the courtesy extended by the Examiner and the Primary Examiner during the interview on October 24, 2000.

Claims 1-37 are pending in the subject application. Claims 8, 9, and 12 have been amended for further clarification purposes, in accord with the Examiner's suggestions. Claims 1, 29 and 33 have been amended to recite that the osteogenic components included in the subject composition are organic. The term "organic" is used in accord with its commonly understood definition: pertaining to carbon-based, non-inert compounds, e.g., proteins or nucleic acids. Support for the use of the term organic is inherently found throughout the instant application. For example, page 6 of the application teaches that DBM, BMP, TGF-β, steroids or other proteins, or combinations thereof can be added to the subject compositions. Those skilled in the art would easily appreciate the use of the term "organic" to describe such compounds. Moreover, the skilled artisan would appreciate the difference between organic and inorganic compounds such as tricalcium phosphate, hydroxyapatite, and other mineral-based compounds. Further, claims 1, 29, and 33 have been amended to recite that the composition "remains at the site of implantation for a sufficient period of time to induce bone formation at said site." Support for this phrase is found at page 5, line 16 and pages 20-21 of the instant application. Claims 1 and 29 have also been amended to positively claim that the composition comprises one or more osteogenic components, to further clarify that

intended to be claimed. Claim 34 has been amended to correct the obvious typographical error. Upon entry of this Amendment, claims 1-39 will be before the Examiner for consideration.

Rejections under 35 USC § 112

2. The Office Action alleges that the metes and bounds of claims 6-13, and 24 cannot be determined due to an open-ended bracket at line 1 of claim 6. Applicants direct the Examiner's attention to line 4 of claim 6 where the closing bracket is placed immediately after the "(ii)". Reconsideration is requested.

3. With respect to the § 112 rejections of claims 8, 9, and 12, Applicants believe that the amendments to these claims obviate the grounds for these rejections. Reconsideration is requested.

4. Claim 30 is rejected under 35 USC § 112, second paragraph for indefiniteness. The Office Action alleges that it is unclear which joints are encompassed by the phrase "other joints." Applicants traverse. The phrase "other joints" is used as a modifier of the preceding term arthrodesis, the meaning of which is well-understood and recognized in the art. Those skilled in the art would fully appreciate and clearly understand what is meant by arthrodesis of a spinal or any other joint.

In addition, claims 28, 36, and 37 are said to be indefinite on the grounds that the definition of U-shaped cannot be determined. Applicants assert that the meaning of U-shaped is intended to pertain to implants that are in the shape of the letter U. Applicants assert that given the level of skill possessed by those skilled in the art, this intended definition would be readily understood and discernible. Applicants respectfully request reconsideration and withdrawal of this 35 USC § 112, second paragraph, rejection of claims 28, 30, 36 and 37.

5. The Office Action alleges that claims 34-37 are indefinite, as claim 34 comprises open brackets. The opening bracket of line 2 is an inadvertent typographical error, and claim 34 has been amended above to remove the bracket. The closing bracket is found immediately after "(ii)" found at line 4 of claim 34. Reconsideration is requested.

Rejections under 35 USC § 102

6. Claims 1-4 and 21 are rejected as anticipated by the Ninomiya reference. Applicants respectfully traverse. In accord with the Examiner's suggestion provided during the October 24th Examiner interview, Applicants note that claim 1 has been amended to positively recite the inclusion of one or more osteogenic components in the claimed composition. As a result of this clarifying amendment, it is clear that the composition referred to in the Ninomiya reference is dramatically different than the claimed composition. However, should the Examiner having any further concerns, Applicants provide hereafter an overview of issues raised in the Office Action as well as Applicants' response to those issues.

The office action alleges that the preparation of the experimental composition as taught in Ninomiya reference does not teach removal of all osteogenic components. Applicants strenuously disagree. The entire experimental design of the Ninomiya reference is based on the removal of all osteogenic components. Indeed, the question that Ninomiya seeks to answer is whether mineralization can occur without the presence of osteogenic components, or, in other words, whether "acellular mineral deposition" (AMD) exists. Accordingly, to answer this question, Ninomiya explicitly teaches that the bone matrix gelatin is treated to "inactivate non-collagenous proteins including BMP." Further, Ninomiya teaches that "[B]one or cartilaginous tissues did not appear around the implants, and also that there were no osteoblast- and osteoclast-like cells in any implants." Further still, Ninomiya teaches that "AMD occurs with no relation to the subsequent bone tissue formation and that NCP never have any roles in AMD process."

In stark contrast, Applicants teach the intentional inclusion of osteogenic components in the subject compositions. The subject composition is intended to generate new bone and/or cartilage tissue via the migration and bioactivation of osteoblast and/or osteoclast cells. Thus, Ninomiya cannot be found to anticipate the claimed invention, as it does not teach all of the elements of the claimed invention as required for an anticipatory reference, and in fact, the reference actually teaches away from the subject matter here sought to be claimed. Reconsideration and withdrawal of this rejection is requested.

7. Claims 1-6, 10-12, 21, 24, 27-30, and 32 stand rejected as anticipated by U.S. Patent No. 4,191,747 to Scheicher. Applicants respectfully traverse. As discussed above, Applicants again point out that claims 1 and 29 have been amended to positively recite the presence of one or more organic osteogenic components in the claimed composition. Applicants assert that these amendments obviate this rejection. Scheicher simply fails to teach or suggest all of the elements of the claims, i.e., inclusion of organic, osteogenic components. With respect to disclosure of a composition comprising components related to bone formation, Scheicher is limited to its teaching at column 3, lines 45 to 68, wherein various inorganic, mineral elements selected from sodium, lithium, carbon, magnesium, boron, fluorine, silicon, phosphorous, calcium, potassium, and/or yttrium ions and/or ions of the rare earths are disclosed. Scheicher contains no disclosure of organic osteogenic substances.

Scheicher does mention the inclusion of "denatured bone meal" in its composition (see column 4, lines 19-41). However, as can be seen from the manner in which the bone meal is prepared, (drying for 8 hours in 100 degrees centigrade, soaking in 20% hydrogen peroxide for 24 hours followed by boiling in hydrogen peroxide, and then sterilizing the bone meal in an autoclave), it is quite clear that any protein-based osteogenic components that may have been present in the bone meal are completely denatured. Scheicher treats the bone meal extremely harshly, and does not in any respect teach or suggest that the denatured bone meal plays any role in inducing new bone formation. It is treated as a passive filler. This is quite distinct from instant claims 1 and 29, wherein it is clear that

organic osteogenic components, such as demineralized bone matrix (DBM) or protein-based growth factors, are intentionally included in the composition in order to induce bone formation.

As demonstrated above, the Scheicher reference does not teach or suggest all of the elements of the claims, as required to be an anticipatory reference. Claims 2-6, 10-12, 21, 24 and 27-28 are dependent on claim 1, and therefore are construed to comprise the limitations of claim 1. Claims 30 and 32 are construed to contain all of the limitations of claim 29. Accordingly, Applicants respectfully request reconsideration and withdrawal of this 35 USC § 102 rejection.

Rejections under 35 USC § 103

8. Claims 1-6, 10-12, 21, 24, 27-30, and 32 are rejected under 35 USC § 103 as being obvious over the Scheicher patent. Applicants traverse. As discussed above, nowhere does Scheicher teach or suggest the inclusion of organic osteogenic components in the composition. The only disclosure in Scheicher dealing with an organic component teaches the harsh and severe treatment, and therefore inactivation, of the organic component before adding it to the composition. This treatment would be counteractive to the use of organic osteogenic components as recited in the present claims. Moreover, there is no suggestion or motivation to modify the teachings of the Schreicher reference to allow for the use of such organic osteogenic components, as required to establish obviousness. Accordingly, reconsideration and withdrawal of this rejection under 35 USC § 103 is requested.

Additionally, or alternatively, this rejection fails because a close inspection of the Scheicher reference reveals that Scheicher does not actually enable the use of gelatin as a carrier. Scheicher generally talks about a composition that comprises a gel-forming agent and mentions that numerous different options of gel-forming agents can be added to the composition. Col. 4, line 42 to col. 5, line 33. However, besides the general statement that gel-forming agents can be added to form concentrations of 0.5-30% (col. 5, lines 32-

33), the only teachings pertaining to specific concentrations of gel-forming agents relate to agarose (the Office Action dated February 28, 2000 even acknowledges that the Scheicher reference is silent as to a concentration for gelatin). More particularly, the only teaching of a specific concentration of agarose is the 2% w/v concentration as taught in Example 1. As a result, Scheicher leaves the skilled artisan having to choose one gel-forming agent from a potentially infinite genus of gel-forming agents, and then determine from a broad genus of concentrations, without any direction, that which is best for that particular gel-forming agent. This conclusion of inadequate enablement is further corroborated by disclosure in the Ammann reference which actually teaches away from the use of gelatin, more on this below.

9. Claims 7, 8, 13-20, 22, 23, and 33-37 are rejected under 35 USC § 103 as obvious over Scheicher in view of Ammann et al. Applicants respectfully traverse. Applicants incorporate herein their remarks above relating to why Scheicher fails to teach or suggest a bone paste composition comprising organic osteogenic components. Ammann teaches a composition that comprises TGF-β and tricalcium phosphate. Ammann also states that a polymer can be added to allow the composition to be molded as needed, wherein gelatin is mentioned as one of the possible polymers that can be used for this purpose.

However, just because Ammann mentions the terms "TGF-β" and "gelatin" does not mean that there is the required teaching or motivation to modify the teachings of Scheicher to achieve a composition using gelatin as a carrier, such that upon implantation, the composition remains at the site of implantation for a sufficient period of time to induce bone formation at said site (see amendments to claims 1 and 29 above). In fact, not only does Ammann fail to cure the aforementioned deficiencies of Scheicher, Ammann actually teaches away from using gelatin as the carrier or gel-forming agent. At column 28, lines 4-5, the Ammann reference specifically teaches that its formulation containing gelatin "melted rapidly and was not easily conformable to the defect" (emphasis added). This statement not only represents an objective indicator of

nonobviousness (a failure by others; see Graham, 148 USPQ 467), it teaches away from the desirability of using gelatin as a carrier agent for osteogenic components.

In spite of Ammann's teaching of the undesirability of using gelatin as a carrier, Applicants' composition purposely comprises gelatin in combination with organic osteogenic components such that the composition remains at the site of implantation for a sufficient amount of time to induce bone formation. This is a clear, superior and unexpected discovery in view of the cited references. The disclosure of Scheicher, in further view of Ammann, simply fails to teach or suggest all of the elements of the rejected claims. Accordingly, in view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration withdrawal of this rejection under 35 USC § 103.

Additionally, or alternatively, this rejection fails because the cited references lack the requisite motivation to modify their teachings to achieve the claimed invention. "[P]rior art references in combination do not make an invention obvious unless something in the prior art references would suggest the advantage to be derived from combining their teachings." *In re Sernaker*, 217 U.S.P.Q. 1, 6 (CAFC 1983). A lack of motivation in the art to combine the cited references is clearly corroborated by the following line of evidence. The Scheicher patent has been public knowledge since at least 1980. DBM has been known and available for over a hundred years, stemming back to the 1880s. Senn, *The American Journal of the Medical Sciences*, **98**:219-243 (1889). Bone morphogenetic proteins and TGF-β have been known and available to the public since at least 1983. See *e.g.* Assoian et al., *J. Biol. Chem.*, **258**:7155 (1983); and Urist, *Science*, **150**:893 (1965). Despite the availability of these references for nearly two decades, the art has lacked the expectation of advantage in combining or modifying these references. Only through hindsight analysis, impermissibly based on the Applicants' own disclosure, does one realize the unexpected and superior results achieved by utilizing gelatin as a carrier for organic osteogenic components.

10. Claims 13, 14, 22, 23, 25, 26, and 33-37 are rejected under 35 USC § 103 (a) as obvious over the Scheicher patent and further in view of U.S. Patent No. 5,484,601 to O'Leary *et al* (O'Leary reference). Applicants respectfully traverse. Applicants incorporate herein the arguments above pertaining to Scheicher and Ammann. Similar to the Ammann reference addressed above, the O'Leary reference fails to cure the deficiencies of the primary reference, Scheicher, and in fact, further teaches away from using gelatin as a carrier.

The O'Leary reference teaches a flowable osteogenic composition that comprises bone powder and a carrier. O'Leary teaches that the carrier is a liquid, synthetic organic material. Gelatin is conspicuously absent from the list of potential carriers provided by O'Leary. The fact that gelatin is not listed as the liquid carrier is not surprising because it clearly does not meet the definition of liquid carrier as defined by O'Leary. At column 3, lines 20-28, O'Leary defines the carrier as being a flowable liquid at 15-40 degrees Celsius when in a "pure or highly concentrated" form. It is commonly understood in the art that gelatin will cross-link and take a solid form at 15 degrees Celsius, even in a highly diluted form (see Wironen Declaration). Thus, following the teachings of O'Leary, the skilled artisan is implicitly directed to avoid the use of gelatin as a carrier because it would not meet the necessary criteria to achieve a flowable composition. O'Leary only mentions the use of gelatin as an optional component to aid in preventing the separation of bone from glycerol.

As discussed previously, Ammann teaches away from the use of gelatin as a carrier. Moreover, the teachings of O'Leary further support this point by directing the skilled artisan away from using gelatin as a carrier. In contrast, claims 1 and 33 pertain to a composition that utilizes gelatin as a primary carrier. Claims 1 and 33 further specify that gelatin is provided in the composition such that the composition remains at the site of implantation for a sufficient period of time to induce formation of bone tissue. Accordingly, the Scheicher reference, alone or in combination with the O'Leary reference, does not establish a *prima facie* case of obviousness for independent claims 1 and 33, or the claims that depend therefrom. Claims 13, 14, 22, 23, 25, and 26 are

dependent on claim 1, and claims 34-37 are dependent on claim 33, and as such, are construed to comprise the limitations of claim 1 or 33, respectively. Therefore, Applicants respectfully request reconsideration and withdrawal of this obviousness rejection under 35 USC § 103.

Objective indicators of nonobviousness: The arguments of novelty and nonobviousness above are further supported by a clear showing of commercial success and wide recognition of superiority of the claimed composition over other products on the market. As Dr. Wironen points out in his declaration (Wironen Declaration to follow with Supplementary Amendment), OSTEOFIL™ (Regeneration Technologies, Inc.) has experienced remarkable commercial success in its short period of time on the market. OSTEOFIL™ relates to a bone past composition that uses gelatin as a carrier for osteogenic substances. Furthermore, Dr. Wironen explains that several recent comparative studies have been conducted which compare the efficacies of the major commercially available osteoinductive bone pastes, including OSTEOFIL™. In sum, these studies revealed that OSTEOFIL™ was the only product which demonstrated significant induction of bone without causing any harmful side effects. See Exhibit C of Wironen Declaration, "An Unexpected Outcome During Testing of Commercially Available Demineralized Bone Graft Materials." While the version of OSTEOFIL™ considered in these studies contained thermally treated gelatin as taught in the copending 09/014,519 application, it still demonstrated the superiority of a gelatin based composition over the other products in the market, e.g., GRAFTON™ (Osteotech, Inc., a glycerol based composition as described in O'Leary). Accordingly, the foregoing remarks establish the presence of two key objective indicators of nonobviousness, and Applicants urge that these indicators further compel a finding of nonobviousness with respect to the rejected claims.

11. Claims 1-37 are provisionally rejected under 35 USC § 103 as being obvious over copending Application No. 09/014519. Applicants traverse. The subject application has an earlier filing date than that of the copending application. As was agreed on in the

October 24th interview, the copending application could not constitute prior art under 35 USC § 102(e), even if it were patented before the subject application. Accordingly, Applicants respectfully request the reconsideration and withdrawal of this obviousness rejection.

Further, Applicants assert that the subject matter contained in copending application no. 09/014519 represents a separate patentable improvement over that disclosed in the subject application. At page 10, the Office Action states that the instant application (example 1, pages 15-16) teaches thermal treatment of gelatin. Applicants assert that the disclosure to which the office action refers involves a completely distinct process than the thermal treatment of gelatin as taught in copending application no. 09/014519. Example 1 of the instant application describes experiments conducted to determine whether processing of collagen at different temperatures would affect the yield of gelatin obtained from the collagen. Applicants showed that as they increased the processing temperature, the yield of gelatin increased but the kinematic viscosity of the gelatin actually decreased. This altering of the gelatin production temperatures is entirely different than the thermal treatment of gelatin taught in copending Application no. 09/014519. If there is any relation, it is that the teachings of example 1 of the instant teach away from the thermal treatment of gelatin as taught in Application no. 09/014519. The thermal treatment of gelatin claimed in 09/014519 is based on Applicant's discovery that subjecting gelatin to much higher temperatures actually changes the structure of the gelatin such that significantly higher kinematic viscosities are possible. These higher kinematic viscosities were demonstrated empirically and by the ability of the gelatin to cross-link at much lower concentrations. See Example 4 and Figure 3 of Application no. 09/014519. Accordingly, in sum, the thermally treated gelatin of copending Application no. 09/014519 is patentably distinct from the teachings of the instant application.

12. Applicants respectfully traverse the provisional obviousness-type double patenting rejection set forth at item 19 of the outstanding office action. Applicants incorporate herein the remarks in item 11 above and reassert that the invention claimed in the subject application and the invention claimed in copending Application no.

09/014519 are patentably distinct from each other. When determining whether a claim of one application is an obvious variation of an invention claimed in another application/patent, the disclosure of the other application/patent may not by used as prior art. *See In re Kaplan*, 229 U.S.P.Q. 678 (Fed. Cir. 1986). The claims of copending application no. 09/014519 are directed to an osteogenic composition that comprises gelatin that has been thermally treated, wherein the thermal treatment provides for an increase in the kinematic viscosity of the gelatin. The composition claimed in the subject application comprises gelatin as a carrier, but the claims do not specify or require that the gelatin be thermally treated. If the disclosure of the 09/014519 application is not used as prior art, no thermal treatment of the gelatin (as that term is used in the 09/014519 application), as opposed to thermal treatment of the gelatin (claims of 09/014519), represents a patentable distinction and is not merely an obvious variation of the claims of the 09/014519 application. Accordingly, Applicants request the reconsideration and withdrawal of this obviousness-type double patenting rejection.

13. The Office Action raises the issue of whether claims 1-37 should be rejected under 35 USC § 103 as obvious by viewing copending application no. 09/014519 as prior art under 35 USC §§ 102(g) and 102(f). Applicants traverse and otherwise believe that their remarks made above asserting the patentable distinctions between the subject application and the copending 09/014519 application obviate this issue altogether. Applicants reiterate that the thermal treatment of gelatin as taught in application no. 09/014519 is a patentable improvement and is clearly distinct from the processing of collagen to produce gelatin. In view of the foregoing, Applicants request the reconsideration and withdrawal of this 35 USC § 103 rejection.

From the preceding remarks, Applicants believe that the currently pending claims are in a condition for allowance, and such action is respectfully requested.

Applicant invites the Examiner to call the undersigned if clarification is needed on any aspect of this response, or if the Examiner believes a telephonic or in-person interview would expedite the prosecution of the subject application to completion. Applicants specifically request for another in-person interview if it is believed that any

claims in this case are not in condition for allowance and cannot be placed in condition for allowance through a telephonic interview.

Respectfully submitted,

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